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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/558,149	04/26/2000	Nicholas Nicolaides	01107.00004	1171
7590	11/02/2006			
Banner & Witcoff Ltd 1001 G Street N W Washington, DC 20001-4597				EXAMINER BERTOGLIO, VALARIE E
				ART UNIT 1632 PAPER NUMBER

DATE MAILED: 11/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)	
	09/558,149	NICOLAIDES ET AL.	
	Examiner Valarie Bertoglio	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 10/02/2006.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 60-62, 71-75, 82, 83, 86, 87, 89, 90, 92 and 93 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 60-62, 71-75, 82, 83, 86, 87, 89, 90, 92 and 93 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 26 April 2000 is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|  | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/02/2006 has been entered.

Claims 1-59,63-70,76-81,84,85,88,91 and 94-96 have been cancelled. Claims 60-62,71,82,89 and 92 have been amended. Claims 60-62,71-75,82,83,86,87,89,90,92 and 93 are pending and under consideration in the instant office action.

#### ***Claim Objections***

Claims 61-63,71,86,89 and 92 are objected to because of the following informalities: Claims 61-63,71,86,89 and 92 use the term “transgenic polynucleotide”. Polynucleotides themselves, however, are not transgenic. Transgenes are polynucleotides that can be introduced as claimed. The terms “transgene” or polynucleotide” would be more appropriate. Appropriate correction is required.

#### ***Claim Rejections - 35 USC § 112-1<sup>st</sup> paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

#### ***New matter***

The rejection of claims 60-62 and 71-75 under 35 USC 1<sup>st</sup>-paragraph for introducing new matter into the specification is withdrawn in light of Applicant's amendments to the claims limiting the dominant negative PMS2 to human PMS2 comprising the first 133 amino acids.

*Enablement*

The previous rejection of claims 60-62, 71-75 and 81-96 under 35 U.S.C. 112, first paragraph as not being enabled by the specification is withdrawn in favor of the following new rejection.

Claims 60-62, 71-75 and 82, 83, 86, 87, 89, 90, 92 and 93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose germ and somatic cells all comprise a gene encoding a dominant negative human PMS2-134 gene product operably linked to a promoter wherein when the transgene is expressed the cells expressing the transgene exhibit hypermutability and for a method of making said mouse comprising introducing into a fertilized mouse egg a polynucleotide encoding a dominant negative human PMS-134 gene operably linked to a promoter wherein the polynucleotide is expressed in cells of the resulting mouse or mouse embryo, does not reasonably provide enablement for the claimed mouse wherein the transgene is not operably linked to a promoter, is not expressed, or for expression and hypermutability in a fertilized egg, *per se*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant has amended the claims to limit the claimed genera of PMS genes. This aspect of the rejection, set forth at pages 8-9 of the office action dated 11/09/2005, is withdrawn in light of Applicant's amendments to the claims. However, the aspect of the rejection regarding embodiments of the claimed invention wherein the transgene is not expressed is maintained as set forth at pages 9-10 of the office action dated 11/09/2005. Furthermore, new grounds of rejection are set forth below regarding the failure of the claims to require operable linkage of the PMS2 gene to a promoter and claims requiring expression and hypermutability in fertilized eggs.

Claim 60 fails to require expression of the PMS2-134 transgene. As set forth at page 9, paragraph 2 –page 10 paragraph 1 of the office action dated 11/19/2005 one would not know how to use the claimed

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mouse that does not express the transgene. Applicant has added limitations to claims 61,62 and 71, however, claim 60 does not recite this limitation and thereby encompasses mice that fail to express the transgene. One of skill in the art would not know how to use the claimed mouse comprising the claimed transgene wherein the transgene is not expressed.

The claims also fail to require the presence of a promoter operably linked to the PMS2-134 gene. The specification has taught operably linking an SV40 promoter to the PMS2-134 gene (page 16, lines 5-7). The specification has not taught expression of PMS2-134 without the operable linkage of a promoter to the desired PMS2-134 gene to be expressed. It was well known in the art at the time of filing that promoter elements are necessary to drive expression of a gene and that the promoter must be placed in a manner to effect expression of a linked gene. Without operable linkage of a gene to a promoter, mere introduction into the genome generally will not lead to expression of the gene unless it integrates, by chance, into the genome under the control of an endogenous gene promoter. Therefore, the claims encompass a PMS2 transgene wherein the transgene is not associated with a promoter through operable linkage. Without such a requirement, the PMS2 gene will not be expressed and, as set forth above, one of skill in the art would not know how to use the claimed mouse without expression of the PMS2-134 transgene.

Claim 61 is a product by process claim and claims 62 and 71 are a method claims drawn to a method of making the above-mentioned mouse. The method steps of the claims require introducing the PMS2-134 transgene into a fertilized egg whereby PMS2-134 protein is expressed in the egg and the egg becomes hypermutable. The specification provides guidance for making the claimed mice by introducing a transgene into fertilized mouse eggs, however, it does not teach expression in and hypermutability of the eggs. The declaration submitted by J. Bradford Kline (04/18/2003) states that the resulting mice were hypermutable. The state of the art at the time of filing was that the mouse zygotic genome is activated at the 2-cell stage [Bonnerot, *Nucl Acids Res*, 19:7251-7257, 1991]. Thus, the specification and the art fail

to support that a fertilized egg, *per se*, injected with the claimed transgene would express the transgene and exhibit hypermutability. Therefore, one of skill in the art would not know how to carry out the method steps of the claims such that PMS2-134 expression and hypermutability occurs in a fertilized egg.

***Claim Rejections - 35 USC § 112-2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 75 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 75 is unclear because of the phrase “phenotype of the gene of interest”. It is not clear whether the claim is literally referring to a phenotype of the gene, itself, as in a characteristic of the nucleic acid (i.e. sequence), or if it is intended to refer to the phenotype of the mouse as an effect of a mutation in the gene of interest.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Valarie Bertoglio  
Examiner  
Art Unit 1632